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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/614,264	07/12/2000	Peter Lohse	50036/028002	2135

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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/614,264	LOHSE ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *14-16 and 19-31* is/are rejected.

7)☒ Claim(s) *17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *20 June 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on June 20, 2002 has been entered as Paper No: 9. The claims pending in this application are claims 1-31 with claims 1-13 withdrawn from consideration as the result of the restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Election/Restriction

2. This application contains claims 1-13 drawn to an invention nonelected with traverse in Paper No. 7 . A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 14-16, 19-26, and 28-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Yanagawa *et al.,* (US patent No. 6,228,994 B1, filed on November 13, 1998).

Yanagawa *et al.,* teach labeled protein and its producing method.

Regarding claim 14, Yanagawa *et al.*, teach a method for analyzing a function of a gene. This method comprised three steps: (1) adding a nucleic acid containing the gene to a cell-free protein synthesis system as a template; (2) carrying out protein synthesis in the presence of a labeling compound such as fluorpur or fluorthiopur (only binding to protein, not RNA) to obtain a protein having the labeling compound attached to the C-terminal of the protein wherein the labeling compound was present at a concentration effective for the labeling compound to bind to the C-terminal of the synthesized protein; and (3) analyzing a function of the labeled protein (for example, see columns 1, 2, and 10). Although Yanagawa *et al.*, did not directly show to form a stalled translation complex recited in step (b) of the claim, in the absence of convincing evidence to the contrary, a translation complex before addition of a puromycin (before peptide was released) are considered as a stalled translation complex since there was a time period that a synthesized protein waited for the puromycin to be added even through this complex only existed in very short time. The peptide was released based on addition of the puromycin (see the attachment).

Regarding claims 15 and 16, the fluorescent tag was attached to the 5'-hydroxy group of a puromycin through a phosphate group (for example, see column 5 and Figure 2).

Regarding claim 19, the vector sequence in plasmid (pT-Trx) was considered as a DNA oligomer that was covalently linked to 3' end of said nucleic acid sequence encoding said protein (thioredoxin with a coding region) (see column 9) since the bond connected the bases in the nucleic acid was 3, 5-phosphodiester bond.

Regarding claims 20-24, 26, and 28, since the labeling compound (tag) could be biotin or fluorescein series (see column 3), the tag was considered as a small molecule and a functional group recited in claims 20-22 and 24. Biotin tag was considered as a tether for attachment to a solid support recited in claim 26 or one member of a specific binding pair recited in claim 28 since it could bind to avidin or streptavidin.

Regarding claim 25, the first function group of said protein was considered as any amino acid in said protein that had a different reactivity from said tag (second functional group such as biotin).

Regarding claim 29, fluorpur or fluorthiopur tag (see Figure 2) was be considered as a phenyl diboronic acid derivative.

Regarding claims 30 and 31, Yanagawa *et al.*, taught puromycin derivatives such as rCpPur (II) or dCpPur (III) or dUpPur (IV) comprising a nucleotide sequence positioned between the tag and puromycin (see Figure 1 and column 10).

Therefore, Yanagawa *et al.*, teach all limitations recited in claims 14-16, 19-26, and 28-31.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagawa *et al.,* (1998) as applied to claims 14-16, 19-26, and 28-31 above, and further in view of Schatz *et al.,* (US Patent No., 5,723,584, published on March 3, 1998).

The teachings of Yanagawa *et al.,* have been summarized previously, *supra.*

Yanagawa *et al.,* did not disclose to attach the tag of a protein having a puromycin label to beads recited in claim 27.

Schatz *et al.,* teach to use streptavidin-coated beads for a wide variety of purposes such as purification of biotinylation peptides (see column 13).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to attach the tag of a protein having a puromycin label to streptavidin-coated beads in view of the reference of Schatz *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Yanagawa *et al.*, and combine above methods together in order to purify the protein with a

puromycin modification using streptavidin-coated beads and further analyze the function of the modified protein (see Yanagawa *et al.,* column 2). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to purify a protein with a puromycin modification using streptavidin-coated beads since this method provided a convenient, efficient, economical way to separate the modified and unmodified protein.

Response to Arguments

In page 10, last paragraph bridging to page 14, first paragraph of applicant's remarks, applicant argued that: (1) "the '994 patent doesn't expressly teach a stalled translation complex," since "[C]laim 14 requires that *translation stalls at the 3' end of the nucleic acid sequence, forming a stalled translation complex comprising the protein and that the stalled translation complex is contacted with the puromycin-tag.*" and "normally there is no translation complex after translation terminates."; (2) the illustrated fluorthiopur compound in the patent of Yanagawa *et al.,* "is not a phenyl diboronic acid derivative; indeed, fluorthiopur does not possess a boron at all."; and (3) "[S]chatz et al., does not provide what Yanagawa lacks" since "[S]chatz does not discuss any method remotely related to Applicant's claimed method for C-terminal protein tagging, nor does it discuss the use of stalled translation complexes in any context.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner agrees that "normally there is no translation complex after translation terminates". However, claim 14 does not limit that a stalled translation complex is formed before a translation terminates. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van*

Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Second, the examiner notes that there is no definition for "a stalled translation complex". During the process of protein synthesis, according to applicant, "[I]mmediately upon termination, the translation complex falls apart, with the two ribosomal subunits disengaging from the mRNA and releasing the protein". Therefore, it is reasonably to consider that a translation complex before addition of a puromycin (before peptide was released) are considered as a stalled translation complex since there was a time period that a synthesized protein waited for the puromycin to be added even through this complex only existed in very short time. The peptide was released based on addition of the puromycin (see the attachment). Third, since the specification does not define what kind of compound can be called as a phenyl diboronic acid derivative, fluorpur or fluorthiopur tag can be considered as a phenyl diboronic acid derivative. Fourth, the examiner agreed with applicant that "[S]chatz does not discuss any method remotely related to Applicant's claimed method for C-terminal protein tagging, nor does it discuss the use of stalled translation complexes in any context.". However, the combination of prior art of Yanagawa *et al.*, and Schatz *et al.*, was used to reject claim 27 and was not used to reject claim 14.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Claims 17 and 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. No claim is allowed.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 308-0196.

Frank Lu
January 27, 2003

Ethan Whisenant, Ph. D.
Primary Examiner (FSA)

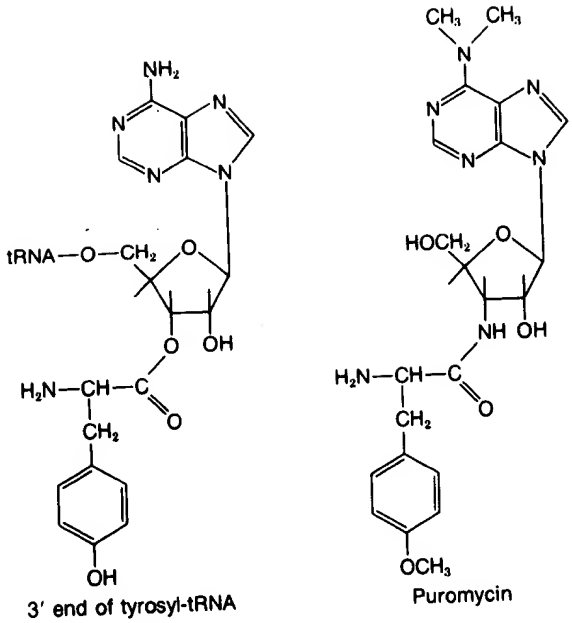

FIGURE 17.12
Puromycin (right) interferes with protein synthesis by functioning as an analog of aminoacyl-tRNA, here tyrosyl-tRNA (left) in the peptidyltransferase reaction.

lation. Resistance to kasugamycin results from the absence of base methylation that normally occurs on two adjacent adenosine residues of small subunit RNA. **Tetracyclines** also bind directly to ribosomes, and function by interfering in aminoacyl-tRNA binding. Hence, several mechanisms of interfering in subunit–tRNA interactions are utilized by different antibiotics.

Other antibiotics function by interfering in peptide bond formation. **Puromycin** (Figure 17.12) resembles an aminoacyl-tRNA; it binds to the ribosomal A site and serves as an acceptor in the peptidyl transferase reaction. However, it cannot be translocated or serve as a peptide donor since its aminoacyl derivative is not in an ester linkage to the nucleoside. Thus puromycin prematurely terminates protein synthesis, leading to release of peptidyl-puromycin. Chloramphenicol directly inhibits peptidyl transferase upon binding at the transferase center; no transfer occurs, and peptidyl tRNA remains associated with the ribosome.

The translocation step is another potential target. **Erythromycin,** a macrolide antibiotic, interferes with translocation by procaryotic ribosomes. Eucaryotic translocation is inhibited by a protein toxin produced by *Corynebacterium diphtheria* **(diphtheria toxin)** through a mechanism in which the toxin binds at the cell membrane and a subunit enters the cytoplasm and catalyzes the **ADP-ribosylation** and inactivation of EF2, as represented in the following reaction.

$$\underset{\text{(active)}}{\text{EF2}} + \text{NAD}^+ \rightleftharpoons \underset{\text{(inactive)}}{\text{ADP-ribosyl EF2}} + \text{nicotinamide} + \text{H}^+$$

Attachment of the ADP-ribose moiety to EF2 is at a specific posttranslationally modified histidine residue known as diphthamide. (Posttranslational events will be discussed in the next section.)

A final group of toxins function by directly attacking the rRNA. The plant toxin **ricin** (from castor beans) and several related toxins are *N*-glycosidases that cleave a single adenine from the large subunit RNA backbone. The ribosome is inactivated by this apparently (to us) minor damage. A fungal toxin, **α-sarcin,** cleaves large subunit RNA at a single site and similarly inactivates the ribosome. Some strains of *E. coli* produce extracellular toxins that affect other bacteria. One of these, colicin